

13 L3(5A)L6
1. 5,643,747, Jul. 1, 1997, Genes for the export of pertussis
holotoxin; Steven M. Baker, et al., 435/69.1, 252.3, 252.33,
320.1; 536/23.7 :IMAGE AVAILABLE:
US PAT NO: 5,643,747 :IMAGE AVAILABLE: L7: 1
of 13
DETDSC:DETD(31)
Identification of B. **pertussis** **toxin** secretion
mutants
L12
1. 5,681,570, Oct. 28, 1997, Immunogenic conjugate molecules;
Yan-ping Yang, et al., 424/197.11, 203.1, 234.1, 244.1, 256.1;
514/54; 536/123.1 :IMAGE AVAILABLE:
2. 5,679,784, Oct. 21, 1997, Recombinant mutants for inducing
specific immune responses; Daniel Iadant, et al., 536/23.7;
424/184.1, 240.1; 435/69.3, 252.3, 320.1 :IMAGE AVAILABLE:
3. 5,667,787, Sep. 16, 1997, Purification of a pertussis
outer membrane protein; Gail Jackson, et al., 424/253.1,
254.1; 530/412, 414, 416, 417, 418 :IMAGE AVAILABLE:
4. 5,648,080, Jul. 15, 1997, Antigenic preparations and
isolation of such preparations; Pavel Novotny, 424/254.1,
184.1, 240.1, 253.1; 530/350, 388.2 :IMAGE AVAILABLE:
5. 5,643,753, Jul. 1, 1997, Use of autologous promoters to
express gene products in bordetella; Sheena Loosmore, et al.,
435/69.3; 424/93.4, 235.1, 240.1, 253.1, 254.1; 435/91.1,
91.4, 91.41, 172.3, 252.3, 320.1; 536/23.7; 935/10, 12, 29,
41, 56, 72 :IMAGE AVAILABLE:
US PAT NO: 5,681,570 :IMAGE AVAILABLE: L12: 1
of 45
DETDSC: DETD(102)
6. Schneerson, R., L. Levi, J. B. Robibin, D. M. Bryla, G.
Schiffman, and T. Lagergard. 1992. Synthesis of a conjugate
vaccine composed of pneumococcus type 14 capsular
polysaccharide bound to **pertussis** **toxin**. Infect.
Immun. 60:3528-3532.
US PAT NO: 5,679,784 :IMAGE AVAILABLE: L12: 2
of 45
DETDSC: DETD(34)
B. **pertussis** AC **toxin** is used to present epitopes of
vaccinal importance to the immune system. This recombinant
toxin may be used as a component of the **vaccine**, either

alone or in the presence of other antigenic preparation(s). It can be used in toxic form or in detoxified. . .

US PAT NO: 5,667,787 :IMAGE AVAILABLE: L12: 3 of 45

SUMMARY: BSUM(5)

This . . . hampered by a lack of information on the mechanism of pathogenesis of B. pertussis. Many virulence associated factors, such as **pertussis** **toxin** (PT), also known as lymphocytosis promoting factor (LPF), filamentous haemagglutinin (FHA), adenylate cyclase, lipopolysaccharide, agglutinogens and other outer membrane proteins have been suggested for inclusion in an "acellular" **vaccine**, which is less defined than the component **vaccine**. Much of the work on acellular vaccines has concentrated on a PT-based **vaccine**. Results of a recent clinical trial have indicated that a **vaccine** consisting entirely of PT-toxoid only partially protected children from the infection. A PT/FHA combination showed slightly higher efficacy but this was still lower than .that obtained for the whole-cell **vaccine**.

CLAIMS:

3. The **vaccine** claimed in claim 2, wherein said at least one other purified immunoprotective pertussis antigen is selected from the group consisting of purified **pertussis** **toxin** (PT), purified filamentous haemagglutinin (FHA) and purified agglutinogens.

9. The method of claim 8 wherein the **vaccine** further comprises, as at least one additional component thereof, at least one other purified antigen of Bordetella pertussis selected from the group consisting of purified **pertussis** **toxin** (PT), purified filamentous haemagglutinin (FHA) and purified agglutinogens.

10. A component **vaccine** against disease caused by infection by Bordetella pertussis, which comprises: as a first component, purified pertactin having no detectable adenylate cyclase activity, as an additional component, at least one other purified B. pertussis antigen selected from the group consisting of **pertussis** **toxin** (PT), filamentous haemagglutinin (FHA) and agglutinogens; and a pharmacologically acceptable carrier therefor.

US PAT NO: 5,648,080 :IMAGE AVAILABLE: L12: 4 of 45

SUMMARY: BSUM(4)

The search for a safer, effectively acellular B. pertussis **vaccine** has been hampered in the past by the paucity of information regarding the identity and mechanisms of action of

the. . . J. Am. Med. Soc., 248 (1) 22-23). Examples of antigens that have been suggested for investigation include lymphocytosis promoting factor (**pertussis** **toxin**/LPF) filamentous haemagglutinin (FHA), lipopolysaccharide (LPS), agglutinogens, dermonecrotic toxin (DNT), heat labile and heat stable toxins, polymorphonuclear leukocyte inhibitor factor, adenylate cyclase and other surface components (Pertussis **Vaccine** Workshop, Feb. 11, 1982, Bureau of Biologics, U.S.A.). Other proposed candidate antigens for investigation include tracheal cytotoxin and various outer. . .

BSUM(7)

Much of the work carried out on acellular pertussis vaccines is concentrated on the possibility of basing such a **vaccine** on LPF. However, it is believed that most (if not all) of the adverse effects hitherto observed to be associated with **pertussis** vaccination are related to the **toxin**. In combination with tetanus or diphtheria toxoid and LPS, it is able to induce experimental encephalopathy in susceptible mice (L. . .

US PAT NO: 5,643,753 :IMAGE AVAILABLE: L12: 5 of 45

SUMMARY: BSUM(4)

The . . . whooping cough with the former generating more severe symptoms. The disease, or vaccination against the disease (using an inactivated whole-cell **vaccine**), elicits antibodies against several antigens, typically **pertussis** **toxin** (PT), filamentous haemagglutinin (FHA), agglutinogens or fimbriae and the 69 kDa outer membrane protein or pertactin. These proteins represent the major immunogens that may be included, individually or in combination, in any **vaccine** used to protect against the disease, whether it be the inactivated whole-cell **vaccine** or a defined component **vaccine**. Therefore, the efficient expression of these antigens from the **vaccine** strain is crucial.

BSUM(7)

The . . . vaccines has resulted in a massive reduction in the incidence of whooping cough since their introduction in the 1950s. These **vaccine** preparations are efficacious but have been known for many years to be reactogenic and to be associated with local and. . . are at various stages of clinical assessment in other countries. Defined pertussis vaccines consist of several combinations of the B.

pertussis-specific antigens **pertussis** **toxin** (PT), filamentous haemagglutinin (FHA), the 69 kDa outer membrane protein (pertactin) and fimbrial agglutinogens. Replacing whole-cell whooping cough vaccines with the defined acellular

preparations has resulted in a substantial increase in the complexity and cost of **vaccine** manufacture. A major portion of these increased costs is due to the relatively low levels of PT and pertactin produced.

L16

1. 5,643,753, Jul. 1, 1997, Use of autologous promoters to express gene products in bordetella; Sheena Loosmore, et al., 435/69.3; 424/93.4, 235.1, **240.1***, 253.1, 254.1; 435/91.1, 91.4, 91.41, 172.3, 252.3, 320.1; 536/23.7; 935/10, 12, 29, 41, 56, 72 :IMAGE AVAILABLE:

US PAT NO: 5,643,753 :IMAGE AVAILABLE: L16: 1 of 29
US-CL-CURRENT: 435/69.3; 424/93.4, 235.1, **240.1***, 253.1, 254.1; 435/91.1, 91.4, 91.41, 172.3, 252.3, 320.1; 536/23.7; 935/10, 12, 29, 41, 56, 72

SUMMARY: BSUM(4)

The . . . severe symptoms. The disease, or vaccination against the disease (using an inactivated whole-cell vaccine), elicits antibodies against several antigens, typically **pertussis** *toxin** (PT), filamentous haemagglutinin (FHA), agglutinogens or fimbriae and the 69 kDa outer membrane protein or pertactin. These proteins represent the. . .

BSUM(6)

Along with other genes, the **pertussis** *toxin** operon (TOX), the filamentous haemagglutinin operon (FHA), and the pertactin gene (PRN) are all positively regulated by the Bordetella virulence.

BSUM(7)

The . . . are at various stages of clinical assessment in other countries. Defined pertussis vaccines consist of several combinations of the B. **pertussis**-*specific antigens **pertussis** *toxin** (PT), filamentous haemagglutinin (FHA), the 69 kDa outer membrane protein (pertactin) and fimbrial agglutinogens. Replacing whole-cell whooping cough vaccines with.

DEDESC: DETD(18)

A pUC-based plasmid (S-3680-10) was constructed which contains the FHA promoter directing the expression of the native **pertussis** *toxin** structural gene and surrounded by the TOX flanking regions (FIG. 1). The FHA promoter is an EcoR I/Hinf I fragment.

DETD(64)

TABLE 1

Production of **pertussis** *toxin** (PT), filamentous haemagglutinin (FHA) and pertactin, from Bordetella pertussis strains that contain hybrid prn alleles at the prn locus. The.

CLAIMS:

What . . . a Bordetella gene fused at the ATG start codon to an autologous Bordetella promoter, wherein: (a) said promoter is the **pertussis** *toxin** operon (TOXp) promoter and the Bordetella gene is selected from the group consisting of the filamentous haemagglutinin operon (FHA) and. . . said promoter is the filamentous haemagglutinin operon (FHAp) promoter and the Bordetella gene is selected from the group consisting of **pertussis** *toxin** operon (TOX) and pertactin (PRN) gene.

3. . . gene fused at an ATG start codon to its own native Bordetella promoter, wherein: (a) said autologous promoter is the **pertussis** *toxin** operon (TOXp) promoter and the Bordetella gene is selected from the group consisting of the filamentous haemagglutinin operon (FHA) and. . . promoter is the filamentous haemagglutinin operon (FHA) promoter and the Bordetella gene is selected from the group consisting of the **pertussis** *toxin** operon (TOX) and pertactin (PRN) gene.

12. . . a Bordetella gene fused at the ATG start codon to an autologous Bordetella promoter, wherein: (1) said promoter is the **pertussis** *toxin** operon (TOXp) promoter and the Bordetella gene is selected from the group consisting of the filamentous haemagglutinin operon (FHA) and. . . said promoter is the filamentous haemagglutinin operon (FHAp) promoter and the Bordetella gene is selected from the group consisting of **pertussis** *toxin** operon (TOX) and pertactin (PRN) gene; (b) introducing said hybrid gene into a Bordetella strain to form a viable transformed

08/483,326

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PASSWORD:

TERMINAL (ENTER 1, 2, 3, 4, OR ?): 3

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* W E L C O M E T O T H E
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* U . S . P A T E N T T E X T F I L E
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*
*
=> d kwic

US PAT NO: 5,705,361 [IMAGE AVAILABLE] L7: 1
of 14

DETD(10)

In . . . and biological activities is a protective antigen. Infect. Immun. 58:3337-3347; and Nencioni, L., et al. 1990. Characterization of genetically inactivated **pertussis** **toxin** **mutants** candidates for a new vaccine against whooping cough. Infect. Immun. 58:1308-1315). However, those methods rely on the purification of detoxified.

US PAT NO: 5,705,361 [IMAGE AVAILABLE] L7: 1
of 14

DATE ISSUED: Jan. 6, 1998
TITLE: Hybrid transposon with PT operon, plasmids and bacterial strains therefor

INVENTOR: Mark Walker, Brunswick, Federal Republic of Germany

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371-DATE: Oct. 21, 1993

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PCT-PUB-NO: WO92/19750
PCT-PUB-DATE: Nov. 12, 1992
FRN-PRIOR: Federal Republic of Germany41 13 385.4
Apr. 24, 1991
INT-CL: [6] C12P 21/02; C12N 1/20; C12N 15/74
US-CL-ISSUED: 435/69.3, 252.3, 320.1
US-CL-CURRENT: 435/69.3, 252.3, 320.1
SEARCH-FLD: 435/320.1, 252.3, 172.3, 69.3; 424/92
REF-CITED:
4,883,761 11/1989 U.S. PATENT DOCUMENTS
435/320.1 Keith et al.

OTHER PUBLICATIONS
Walker et al., Infection and Immunity, vol. 59, Nov. 1991, pp. 4238-4248.
Herrero et al., V. Bacteriol., vol. 172, Nov. 1990, pp. 6557-6567.
Bloom, Rev. Infect. Diseases, vol. 11, Supplement 2, 1989, pp. 5460-5466.
Knapp et al., vol. 170, J. Bacteriol., 1988, pp. 5059-5066.
ART-UNIT: 185
PRIM-EXMR: James S. Ketter
LEGAL-REP: Kane, Dalsimer, Sullivan, Kurucz, Levy, Eisele and Richard

ABSTRACT:

The invention relates to a hybrid transposon having a PT operon, to plasmids and to bacterial strains (hosts) therefor.
12 Claims, 4 Drawing Figures

=> d clm

US PAT NO: 5,705,361 [IMAGE AVAILABLE] L7: 1
of 14

CLAIMS:

CLMS(1)

We claim:

1. A plasmid for the stable expression of pertussis toxin in a bacterial microorganism which comprises;

a promoterless hybrid transposon wherein a transposase gene is arranged outside of inverted repeats of the transposon; and having a pertussis toxin operon inserted between the inverted repeats;
said inverted repeats being in shortened form, thereby permitting a further transposition;
said plasmid permitting a stable insertion of the pertussis toxin operon into a bvg-negative bacterial strain.

CLMS(2)

2. A plasmid according to claim 1 wherein the transposon is a mini-transposon.

CLMS(3)

3. A plasmid according to claim 1 wherein the transposon is from Tn5 and the inverted repeats each have a length of approximately 19 base pairs.

CLMS(4)

4. A plasmid according to claim 1 wherein the operon is selected from the group consisting of a wild-type operon and an operon that encodes a pertussis toxin modification effective against whooping cough.

CLMS(5)

5. A plasmid according to claim 1 wherein the hybrid transposon contains a kanamycin resistance gene.

CLMS(6)

6. A plasmid which is promoterless having the following features and is a suicide vector that has a mini-transposon for pertussis toxin

expression for transcriptional fusions with native promoters, having
1. a mob site,
2. an ampicillin resistance gene and
3. in each case, 19 base pairs of the terminal Tn5 end which flank,

4. a kanamycin resistance gene and
5. a promoterless operon; and also having
6. a IS50.sub.R -transposase gene.

CLMS (7)

7. A bvg-negative bacterial strain containing a plasmid according to claim 1.

CLMS (8)

8. The bacterial strain of claim 7 which is selected from the group consisting of Bordetella pertussis, Bordetella parapertussis and Bordetella bronchiseptica.

CLMS (9)

9. A bvg-negative bacterial strain wherein a pertussis toxin operon has been incorporated by means of a plasmid according to one of claims 1, 2 and 3 to 6.

CLMS (10)

10. The strain of claim 9 selected from the group of species consisting of Bordetella pertussis, Bordetella parapertussis and Bordetella bronchiseptica.

CLMS (11)

11. The strain of claim 10 which is Bordetella bronchiseptica ATCC 10580.

CLMS (12)

12. A process for the stable expression of pertussis toxin which comprises; culturing a bvg-negative bacterial strain containing a plasmid according to one of claims 1, 2 and 3 to 6.

=> s (arg or arginine) (w)9 or arg9 or arginine9

8246 ARG
13998 ARGinine
1660508 9

49 (ARG OR ARGinine) (W)9
8 ARG9

1 ARGinine9

L8 57 (ARG OR ARGinine) (W)9 OR ARG9 OR ARGinine9

=> s 18(p)11

L9 1 L8(P)L1

=> s 13 and 18

L10 1 L3 AND L8

=> s vaccine

L11 4528 VACCINE

=> s 111(p)13

L12 48 L11(P)L3

=> d 1-3

1. 5,725,860, Mar. 10, 1998, Method for reducing the risk of developing diabetes; Robert Bartlett Elliott, 424/240.1; 514/2, 21 [IMAGE AVAILABLE]

2. 5,705,361, Jan. 6, 1998, Hybrid transposon with PT operon, plasmids and bacterial strains therefor; Mark Walker, et al., 435/69.3, 252.3, 320.1 [IMAGE AVAILABLE]

3. 5,695,766, Dec. 9, 1997, Highly virulent porcine reproductive and respiratory syndrome viruses which produce lesions in pigs and vaccines that protect pigs against said syndrome; Prem S. Paul, et al., 424/204.1, 209.1, 218.1, 815; 435/235.1, 236, 237, 238, 239 [IMAGE AVAILABLE]

=> d kwic

DETD(45)

SUMMARY:

The conclusions we draw from this are that the pertussis vaccine is the active adjuvant in the mixed, triple vaccine, and that diphtheria and tetanus vaccine are without effect. It also appears that A-chain itself, or in combination with diphtheria and/or tetanus vaccine is ineffective. The pertussis vaccine used was a "cellular" vaccine containing many defined, and some undefined components, and so we are unable to specify which component or components of the vaccine contain(s) the active principle. Indeed, diphtheria and/or tetanus vaccines may be required in addition as "co-factors". It may be relevant that for a long time pertussis toxin has been known to stimulate insulin secretion from the islets of Langerhans, probably through the "G protein" control sequence.

=> d 2-3 kwic

SUMMARY:

BSUM(3)

The invention relates to a plasmid for bacterial expression of pertussis toxin, useful in vaccine preparation.

SUMMARY:

BSUM(5)

Increasing incidence has in turn resulted in an increase in the incidence of the disease. It is imperative that an effective, nonreactogenic vaccine of high acceptability be developed. Several potentially protective antigens are candidates for inclusion in a purified multi-component vaccine, including toxins, such as pertussis toxin (PT) and adenylate cyclase, and also several cell surface or secreted antigens like filamentous haemagglutinin and serotype-specific fimbriae (Robinson, A., et al. 1985. Pertussis vaccine: present status and future prospects. Vaccine 3:11-22; and Robinson, A., and I. A. E. Ashworth. 1988. Acellular and defined-component vaccines against pertussis, p. 399-417. In A. . . is hampered by antigenic variation controlled by the bvg-positive regulatory locus (Gross, R., and R. Rappuoli. 1988. Positive regulation of pertussis toxin expression. Proc. Natl. Acad. Sci. 85:3913-3917; Knapp, S., and J. J. Mekalanos. 1988. Two trans-acting regulatory genes (vir and mod) . . . under the control of the lambda P.sub.L promoter (Burnette, W. N., et al. 1988. Direct expression of Bordetella pertussis toxin subunits to high levels in Escherichia coli. Biotechnol. 6:699-706). The serotype 2 fimbrial sub-unit has also been expressed with the . . . also extremely unstable, being subject to both plasmid loss and gene deletions (Locht, C., et al. 1986. Molecular cloning of pertussis toxin genes. Nucl. Acids Res. 14:3251-3261).

DETD(10)

DETD(10)

In . . . that methods for the genetic detoxification of PT have recently been developed by several groups (Kimura, A., et al. 1990.

Pertussis **toxin** analog with reduced enzymatic and biological activities is a protective antigen. Infect. Immun. 58:3337-3347; and Nencioni, L., et al. 1990. Characterization of genetically inactivated **pertussis** **toxin** mutants: candidates for a new **vaccine** against whooping cough. Infect. Immun. 58:1308-1315). However, those methods rely on the purification of detoxified PT from B. pertussis. The . . of bvg-negative strains of B. bronchiseptica in combination with methods for the genetic detoxification of PT will lead to a **vaccine** component of high purity and low reactogenicity.

US PAT NO: 5,695,766 [IMAGE AVAILABLE] L12: 3 of 48

DETDESC:

DETD(51)

The composition containing the present **vaccine** may be administered in conjunction with an adjuvant. An adjuvant is a substance that increases the immunological response to the present **vaccine** when combined therewith. The adjuvant may be administered at the same time and at the same site as the **vaccine** or at a different time, for example, as a booster. Adjuvants also may advantageously be administered to the animal in a manner or at a site or location different from the manner, site or location in which the **vaccine** is administered. Adjuvants include aluminum hydroxide, aluminum potassium sulfate, heat-stable enterotoxin isolated from Escherichia coli, cholera toxin or the B subunit thereof, diphtheria **toxin**, tetanus **toxin**, **pertussis** **toxin**, Freund's incomplete adjuvant, Freund's complete

adjuvant, and the like. Toxin-based adjuvants, such as diphtheria **toxin**, tetanus **toxin** and **pertussis** **toxin**, may be inactivated prior to use, for example, by treatment with formaldehyde.

=> s (514/12 or 424/240.1 or 424/190.1 or 424/94.5)/ccls

1716 514/12/CCLS
45 424/240.1/CCLS
80 424/190.1/CCLS

61 424/94.5/CCLS

L13 1882 (514/12 OR 424/240.1 OR 424/190.1 OR 424/94.5)/CCLS

=> s l3 and l13

L14 47 L3 AND L13

=> d 1-3

1. 5,736,143, Apr. 7, 1998, Anti-inflammatory, tolerogenic and immunoinhibiting properties of carbohydrate binding-peptides; Louis D. Heerze, et al., **424/190.1***, 275.1; 514/885 [IMAGE AVAILABLE]

2. 5,731,151, Mar. 24, 1998, Regulator of contact-mediated hemolysin; C. Harold King, et al., 435/6; **424/190.1***, 200.1, 248.1; 435/41, 69.1, 71.1; 536/25.3 [IMAGE AVAILABLE]

3. 5,725,860, Mar. 10, 1998, Method for reducing the risk developing diabetes; Robert Bartlett Elliott, **424/240.1***, 514/2, 21 [IMAGE AVAILABLE]

=> s (toxin/clm) or holotoxin/clm or s1/clm

724 TOXIN/CLM
9 HOLOTOXIN/CLM
1280 S1/CLM

L15 1997 (TOXIN/CLM) OR HOLOTOXIN/CLM OR S1/CLM

=> s l14 and l15

L16 29 L14 AND L15

=> d his

(FILE 'USPAT' ENTERED AT 13:58:18 ON 04 MAY 1998)

L1 1133 S PERTUSSIS
L2 4029 S TOXIN
L3 226 S L1(5N)L2
L4 411817 S MUTAT? OR SUBSTITUT? OR MUTAN? OR MUTAGEN?
L5 572562 S REPLAC?
L6 832228 S L4 OR L5
L7 14 S L3(5N) L6
L8 57 S (ARG OR ARGinine) (W) 9 OR ARG9 OR ARGinine9
L9 1 S L8(P)L1
L10 1 S L3 AND L8
L11 4528 S VACCINE
L12 48 S L11(P)L3
L13 1882 S (514/12 OR 424/240.1 OR 424/190.1 OR
424/94.5)/CCLS
L14 47 S L3 AND L13
L15 1997 S (TOXIN/CLM) OR HOLOTOXIN/CLM OR S1/CLM
L16 29 S L14 AND L15

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